Plasma Levels of MCP-1 and Adiponectin in Obstructive Sleep Apnea Syndrome

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Objectives: To evaluate the correlation between concentrations of the proinflammatory cytokines monocyte chemotactic protein 1 (MCP-1), adiponectin, interleukin 6 (IL-6), interleukin 8 (IL-8), and tumor necrosis factor (TNF) and patients with obstructive sleep apnea syndrome (OSAS). Repeated apnea attacks in patients with OSAS constitute a hypoxic condition, which induces tissue inflammation by mediation of these proinflammatory cytokines.

Design: Radioimmunoassay analyses of nonrandomized controlled trial.

Setting: University-affiliated tertiary care hospital.

Patients: The study population comprised 59 patients who underwent the polysomnography.

Main Outcome Measures: Serum concentrations of MCP-1, adiponectin, IL-6, IL-8, and TNF, as well as body mass index and polysomnographic data, including apnea-hypopnea index (AHI) and lowest oxygen saturation.

Results: The mean (SD) plasma level of MCP-1 in serum was increased in all patients with OSAS ($P < .001$), while adiponectin level was decreased in the patients with severe OSAS (6.88 [1.78] µg/mL) compared with normal controls (8.90 [2.63] µg/mL) ($P = .006$). Serum concentrations of IL-6, IL-8, and TNF did not exhibit any differences between patients with OSAS and normal controls. The correlation coefficient between plasma MCP-1 level and AHI was 0.62 and between adiponectin level and AHI was 0.66.

Conclusions: Our results suggest that plasma MCP-1 and adiponectin levels were different between patients with OSAS and normal controls. Adiponectin and MCP-1 may be prognostic factors for comparing patients with OSAS before and after treatment.


Obstructive sleep apnea (OSA) repeatedly causes low oxygen ($O_2$) saturation during sleep. This causes functional abnormality in vascular endothelial cells and increases the risk of cardiovascular diseases such as atherosclerosis. Hypoxia is known to be associated with a series of inflammatory responses through the induction of adhesion molecules and C-reactive protein in vascular endothelial cells and leukocytes. Obstructive sleep apnea is also involved in various metabolic dysfunctions such as insulin resistance with or without obesity. Despite an increased heart rate, circulating blood flow, $O_2$ consumption, and overall blood flow in patients with severe obesity do not change and the $O_2$ level in the arterial blood is relatively decreased. Moreover, enlarged adipose cells need more $O_2$, hypoxic condition gradually induces tissue inflammation, and adipose tissues release materials to overcome cardiovascular disease.

Monocyte chemotactic protein 1 (MCP-1) is the cytokine that integrates the migration of leukocytes or monocytes to inflammatory tissue. A transient or repeated hypoxia induced by OSA increases the cellular adhesion of inflammatory cells and results in the atherosclerosis by the mediation of this proinflammatory cytokine in vascular endothelial cells. Adiponectin, one of the materials released from adipose cells, has an anti-inflammatory effect. Its plasma concentration is low in patients with obesity compared with healthy individuals. This has been known to affect the increased prevalence of cardiovascular diseases. Chronic hypoxic condition also contributes to the low level of adiponectin. Serum adiponectin has been reported to be decreased in patients with sleep apnea with a high apnea-hypopnea index (AHI). Some famous proinflammatory cytokines such as interleukin 6 (IL-6), interleukin 8 (IL-8), and tumor necrosis factor (TNF) were proven to raise the risk of developing cardiovascular disease.

Although there have been so many studies that deal with cytokines, especially adiponectin, the studies on other hypoxia-sensitive molecules such as MCP-1, IL-6, and TNF are hard to find. The purpose of the present study was to examine proinflammatory cytokines such as...
MCP-1, IL-6, IL-8, and TNF, as well as adiponectin in patients with OSA syndrome (OSAS) and define the correlation between such cytokines and the severity of OSAS.

METHODS

Among the patients who had visited the department of otolaryngology clinic for evaluation of sleep problems, 59 were selected. Polysomnography (PSG) was performed in all the patients, and 37 patients were diagnosed as having OSAS, with an AHI exceeding 5. History of diabetes, hypertension, or chronic pulmonary disease was checked by blood test and radiologic evaluation, and those with any of these conditions were excluded. The patients with other cardiovascular disease and metabolic disorders were excluded as well.

Apnea was defined as a complete lack of air flow for at least 10 seconds. Hypopnea was defined as a decreased O2 saturation by more than 4% for at least 10 seconds. Apnea-hypopnea index was defined as the frequency of apnea and hypopnea per 1 hour. We defined OSAS as cases in which AHI exceeded 5. Moderate severity was classified in patients whose AHI ranged between 5 and 20. Severe OSAS was defined when AHI exceeded 20. Patients in the normal control group consisted of those who had an AHI lower than 5 and no complaint of sleep apnea. Body mass index (BMI), a statistical measurement that compares a person’s weight and height, was calculated as weight in kilograms divided by the height in meters squared.

Blood sampling was performed prior to PSG at 8 to 10 pm. After 10 minutes of centrifugation, plasma was isolated. For measurement of the concentrations of MCP-1, adiponectin, IL-6, IL-8, and TNF in plasma, a radioimmunoassay was performed using Human Adipokine Kit (Linco Research Inc, St Charles, Missouri). Each specimen was diluted 1-, 2-, and 4-fold. Assay buffer and mixed beads were added in a microwell whose surface was coated with antibodies against anti-human MCP-1, adiponectin, IL-6, IL-8, and TNF. The reaction was performed at room temperature for 2 hours. After rinsing, each antibody was added for conjugation to the enzyme. This reaction was performed at room temperature for more than 1 hour. By adding enzyme substrate solution, the reaction was performed at room temperature for approximately 30 minutes. After adding the stopping solution, the absorbance was measured using an enzyme-linked immunosorbent assay (ELISA) plate reader at a wavelength of 450 nm.

Statistical analysis was carried out using SPSS version 12.0 software program (SPSS Inc, Chicago, Illinois) and bivariate correlation test was used to determine the relation between each cytokine and sleep apnea. A coefficient of correlation was obtained with the same program. Statistical significance was set at a P value of .01. Informed consent was obtained from all participants, and our institutional review board approved this study.

RESULTS

A total of 48 male and 11 female patients were analyzed. The mean age was 36 years. The normal control group consisted of 21 patients with normal findings on PSG. Among 37 patients, 28 with an AHI exceeding 20 on PSG were classified as the severe OSAS group and 9 with an AHI less than 20 as the moderate OSAS group.

The mean (SD) BMI of the normal control, moderate, and severe OSAS groups were 23.88 (2.30), 24.43 (2.45), and 28.69 (4.05), respectively. There were no statistical differences among the groups. The mean (SD) minimal O2 saturation of the moderate OSAS group was 85.67% (3.30%) compared with 74.79% (6.86%) in the severe group (Table). The serum concentration of MCP-1, adiponectin, IL-6, IL-8, and TNF are also given in the Table.

The serum concentration of MCP-1 of the normal control group was lower than that of the OSAS groups (P < .001), and the difference between the 2 OSAS groups was statistically significant (P < .001). The mean (SD) adiponectin level of normal control was 8.90 (2.63) pg/mL, which was higher than that of the severe OSAS group with a statistical significance (P = .006). However, there was no difference between normal controls and the moderate OSAS group (P = .25). There were no differences among groups in serum concentrations of IL-6, IL-8, and TNF (P = .21, .38, and .18, respectively).

Between the 2 OSAS groups, serum concentration of MCP-1 was positively correlated with BMI (r = 0.59) and AHI (r = 0.62) after bivariates analysis (Figure 1). Serum adiponectin was positively correlated with BMI (r = 0.44) and AHI (r = 0.66) (Figure 2).

COMMENT

Repeated hypoxic condition in the patients with OSAS resulted in a change of plasma concentration of TGF-β-type cytokine originating from immune cells in peripheral blood.11,12 It is also proved that hypoxia increases the expression of proinflammatory molecules such as IL-1β, IL-6, and TNF.13,14 The patients with metabolic disorder, including obesity, showed increased expression of IL-6, IL-8, and TNF, and elevated levels of these cytokines increase the possibility of cardiovascular diseases.15,16 The repeated OSA attacks aggravate hypoxia, especially in enlarged adipose tissue, and this induces more proinflammatory cytokines in plasma. Obese patients are usually exposed to the hypoxic condition without any increased blood flow, although they need more O2 consumption because of increased body mass. It has been reported that hyperventilation, which increases the level of O2 saturation, or the use of continuous positive airway pressure for the management of OSAS will decrease the plasma level of these cytokines in several

### Table. Mean (SD) Measurements in Each Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n=22)</th>
<th>Moderate OSAS (n=9)</th>
<th>Severe OSAS (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>26 (6.91)</td>
<td>38 (15.04)</td>
<td>42 (10.77)</td>
</tr>
<tr>
<td>BMI</td>
<td>23.88 (2.30)</td>
<td>24.43 (2.45)</td>
<td>28.69 (4.05)</td>
</tr>
<tr>
<td>AHI</td>
<td>1.25 (1.25)</td>
<td>14.40 (4.07)</td>
<td>52.71 (22.23)</td>
</tr>
<tr>
<td>Lowest oxygen saturation, %</td>
<td>93.60 (3.18)</td>
<td>85.67 (3.30)</td>
<td>74.79 (6.86)</td>
</tr>
<tr>
<td>Adiponectin, µg/mL</td>
<td>8.90 (2.63) a</td>
<td>8.08 (1.66) a</td>
<td>6.88 (1.78) a</td>
</tr>
<tr>
<td>MCP-1, pg/mL</td>
<td>32.80 (15.93)</td>
<td>71.11 (35.39) a</td>
<td>111.14 (35.50) a</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>3.02 (2.44)</td>
<td>2.87 (2.53)</td>
<td>3.57 (2.74)</td>
</tr>
<tr>
<td>IL-8, pg/mL</td>
<td>12.89 (4.30)</td>
<td>11.90 (2.65)</td>
<td>13.35 (5.63)</td>
</tr>
<tr>
<td>TNF, pg/mL</td>
<td>14.40 (4.13)</td>
<td>14.58 (5.61)</td>
<td>15.32 (6.80)</td>
</tr>
</tbody>
</table>

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IL, interleukin; MCP-1, monocyte chemotactic protein 1; OSAS, obstructive sleep apnea syndrome; TNF, tumor necrosis factor.

a Statistically significant at P < .01 (by unpaired t test).
Monocyte chemotactic protein 1 is one of the proinflammatory cytokines that facilitates leukocyte migration to inflamed tissue by leukocyte’s ability to adhere to microvascular endothelium. It is upregulated in human atherosclerotic plaques, suggesting a role in the development of atherosclerotic lesions. Monocyte chemotactic protein 1 is also known to have a strong correlation in the patients with diabetes or obesity. Ohga et al showed that MCP-1 levels were increased in patients with OSAS compared with normal controls. These authors also noted that MCP-1 levels were decreased after the use of continuous positive airway pressure. Hayashi et al reported on its close relationship with BMI, although there was no significant correlation between MCP-1 and BMI. Our series showed a correlation coefficient of 0.62 between the MCP-1 and AHI, which is similar to their result of the positive correlation with BMI. AHI indicates apnea-hypopnea index; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MCP-1, monocyte chemotactic protein 1.

Adiponectin, one of the various adipocyte-derived biologically active peptides, has received considerable attention owing to its association with several cardiovascular risk factors. Some diseases such as coronary heart disease, dyslipidemia, insulin resistance, and type 2 diabetes mellitus were shown to be related to reduced plasma adiponectin levels. The presence of adiponectin might have an effect on obesity or metabolic diseases in patients with OSAS. Wolk et al reported that adiponectin levels compared with the more severe ones (P <.001). There was no difference in the serum level of adiponectin between patients with OSA and the normal control group. These authors also noted that there was a significant correlation between serum adiponectin level and age. Controversial opinions still exist regarding adiponectin in patients with OSAS. In our series, adiponectin had a stronger correlation with AHI (r =.066) compared with age and BMI (r =.35) or BMI and AHI (r =.44). These results indicate that adiponectin has more influence on AHI compared with other factors in patients with OSAS.

Interleukin 6, IL-8, and TNF are well-known proinflammatory cytokines that are proven to be elevated in patients with OSAS and have been proposed as the mediators of muscle weakness. Interestingly, there were no significant correlations between their concentrations and AHI. Presumably, this might be the result of their short half-life and instability to the stimulation.

There were some differences in plasma concentration between the OSAS groups. The serum level of MCP-1 in the normal control group was lower than in the OSAS groups, and the less severe patients had higher serum MCP-1 levels compared with the more severe ones (P <.01). There was no difference in the serum level of adiponectin between the moderate and severe OSAS groups (P =.10), whereas that of the normal control group was higher than in the severe group (P =.006). There were also no differences between groups in serum levels of IL-6, IL-8, and TNF.

Generally, Asian people have more frequent hypoxic events compared with white people with comparable BMIs because of their physical characteristics. According to Li et al, Asian people had a mean (SD) AHI of 36.6 (34.9), with a BMI of 26.6 (3.7), whereas white people had an AHI of 100. Moreover, the change of serum level of proinflammatory cytokines will be helpful in monitoring the efficacy of treatment of OSAS.

Hayashi et al reported on its close relation-ship with BMI, although there was no significant correlation between MCP-1 and BMI. Our series showed a correlation coefficient of 0.62 between the MCP-1 and AHI, which is similar to their result of the positive correlation with BMI. AHI indicates apnea-hypopnea index; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MCP-1, monocyte chemotactic protein 1.

**Figure 1.** A, Scatterplot of correlation between the plasma level of MCP-1 and AHI in the patients with obstructive sleep apnea syndrome; B, correlation between MCP-1 and BMI. AHI indicates apnea-hypopnea index; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

**Figure 2.** A, Scatterplot of correlation between the plasma level of adiponectin and AHI in the patients with obstructive sleep apnea syndrome; B, correlation between adiponectin and BMI. AHI indicates apnea-hypopnea index; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).
of 55.6 (26.9), with BMI of 30.7 (5.9). That is to say, compared with whites, Asians with a lower BMI had approximately the same AHI. Scharf et al.28 reported that the mean (SD) BMI was 33.4 (9.2) and mean (SD) AHI was 33.4 (26.8) in whites. In our series, mean (SD) BMI was 32.71 (22.23), with a mean (SD) BMI of 28.69 (4.05) in the severe OSAS group, a result that is similar to Asians in the report by Li et al.28 The population who were diagnosed as having severe OSAS without a high degree of obesity is relatively greater compared with that of whites without a high degree of obesity. A greater number of patients with higher AHIs and the same BMI as whites suggests that the diagnosis and treatment should be performed based on the different criteria from whites in the Asian clinical setting.

Recently, PSG became a first choice for the diagnosis of sleep disorder. However, its use is limited because it is expensive and inconvenient and needs special facilities and a specialist for analysis. Adiponectin and MCP-1 can be more reasonable alternatives to PSG for predicting the prognosis and confirming the effect of treatment because of their convenience and cost-effectiveness. The concentration of serum MCP-1 had a greater change in measurement according to the severity of OSAs than adiponectin. Accordingly, MCP-1 might be more useful as an indicator for predicting the occurrence of OSA than adiponectin.

Body mass index, our primary measure of obesity, usually does not fully characterize the distribution of body fat, and the distribution of BMI is not homogenized in each subgroup. This makes it difficult to confirm the independent effects of obesity or AHI in each group. For the clinical application, a systematized investigation to identify the correlations between obesity and proinflammatory molecules, and a larger-scale study with quantitative measurements is warranted.

In conclusion, patients with OSAS had a relatively higher serum MCP-1 level and a lower adiponectin level compared with the normal control group. Adiponectin and MCP-1 are associated with OSAS and might be useful indicators for comparing the postoperative and preoperative status and estimating the prognosis.

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Analysis and interpretation of data: Park and B. G. Kim.

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Critical revision of the manuscript for important intellectual content: J. Kim, S. W. Kim, and Cho.

Statistical analysis: Park and B. G. Kim.

Administrative, technical, and material support: Lee.

Study supervision: J. Kim, S. W. Kim, and Cho.

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REFERENCES


